

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOSTAVAX safely and effectively. See full prescribing information for ZOSTAVAX.

ZOSTAVAX® Zoster Vaccine Live Suspension for subcutaneous injection

Initial U.S. Approval: 2006

INDICATIONS AND USAGE

ZOSTAVAX® is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older (1). ZOSTAVAX is not indicated for the treatment of zoster or postherpetic neuralgia (PHN) (1).

DOSAGE AND ADMINISTRATION

Single 0.65 mL subcutaneous injection (2.1)

DOSAGE FORMS AND STRENGTHS

Single dose vials with not less than 19,400 plaque-forming units [PFU] per 0.65 mL dose when reconstituted to a suspension (2.1, 3, 16).

CONTRAINDICATIONS

- History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine (4.1).
- History of primary or acquired immunodeficiency states (4.2).
- On immunosuppressive therapy (4.2).
- ZOSTAVAX is not indicated in women of child-bearing age and should not be administered to pregnant females (4.3, 8.1, 17.1).

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose and Schedule
- 2.2 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypersensitivity
- 4.2 Immunosuppression
- 4.3 Pregnancy

5 WARNINGS AND PRECAUTIONS

- 5.1 Transmission of Vaccine Virus
- 5.2 Primary Varicella Disease
- 5.3 Preventing and Managing Allergic Vaccine Reactions
- 5.4 Limitations of Vaccine Effectiveness
- 5.5 Concurrent Illness

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

WARNINGS AND PRECAUTIONS

- ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox) (5.2, 8.4).
- Transmission of vaccine virus may occur rarely between vaccinees and susceptible contacts (5.1).
- Defer vaccination in patients with active untreated tuberculosis (5.5).

ADVERSE REACTIONS

The rate of serious adverse events (SAEs) from Days 0 to 42 postvaccination may be increased in recipients of ZOSTAVAX compared to recipients of placebo (Table 1, 6.1.1).

The most frequent vaccine-related adverse events, reported in ≥1% of subjects vaccinated with ZOSTAVAX, were headache and injection site reactions (6.1.1).

To report vaccine exposure during pregnancy call 1-800-986-8999.

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or VAERS at 1-800-822-7967 and www.fda.gov/vaers.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2009

7 DRUG INTERACTIONS

- 7.1 Concomitant Administration with Other Vaccines

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Instructions
- 17.2 FDA-Approved Patient Labeling

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZOSTAVAX¹ is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older.

ZOSTAVAX is not indicated for the treatment of zoster or postherpetic neuralgia (PHN).

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2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

ZOSTAVAX should be administered as a single 0.65 mL dose subcutaneously in the deltoid region of the upper arm.

Do not inject intravascularly or intramuscularly. Use only sterile syringes free of preservatives, antiseptics, and detergents for each injection and/or reconstitution of ZOSTAVAX. Preservatives, antiseptics and detergents may inactivate the vaccine virus.

2.2 Preparation for Administration

ZOSTAVAX is stored frozen and should be reconstituted immediately upon removal from the freezer. The diluent should be stored separately at room temperature or in the refrigerator.

Use separate sterile needles for reconstitution and administration of ZOSTAVAX.

To reconstitute the vaccine: Use only the diluent supplied. Withdraw the entire contents of the diluent into a syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly.

ZOSTAVAX when reconstituted is a semi-hazy to translucent, off-white to pale yellow liquid.

Withdraw the entire contents of reconstituted vaccine into a syringe and inject the total volume subcutaneously.

THE VACCINE SHOULD BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY.

DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

DO NOT FREEZE RECONSTITUTED VACCINE.

Needles should be disposed of properly and should not be recapped.

3 DOSAGE FORMS AND STRENGTHS

ZOSTAVAX is a lyophilized preparation of live, attenuated varicella-zoster virus (Oka/Merck) to be reconstituted with sterile diluent to give a single dose suspension with a minimum of 19,400 PFU (plaque forming units) when stored at room temperature for up to 30 minutes.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer ZOSTAVAX to individuals with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin or any other component of the vaccine. Neomycin allergy manifested as contact dermatitis is not a contraindication to receiving this vaccine.¹

4.2 Immunosuppression

Do not administer ZOSTAVAX to individuals with a history of primary or acquired immunodeficiency states including leukemia; lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or AIDS or other clinical manifestations of infection with human immunodeficiency viruses. ZOSTAVAX is a live attenuated varicella-zoster vaccine and administration may result in disseminated disease in individuals who are immunosuppressed. Do not administer ZOSTAVAX to individuals on immunosuppressive therapy.

4.3 Pregnancy

ZOSTAVAX is not indicated in women of child-bearing age and should not be administered to pregnant females [*see Pregnancy (8.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Transmission of Vaccine Virus

Transmission of vaccine virus may occur rarely between vaccinees and susceptible contacts.

5.2 Primary Varicella Disease

ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox).

5.3 Preventing and Managing Allergic Vaccine Reactions

As with any vaccine, adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic/anaphylactoid reaction occur.

5.4 Limitations of Vaccine Effectiveness

The duration of protection beyond 4 years after vaccination with ZOSTAVAX is unknown. The need for revaccination has not been defined.

Vaccination with ZOSTAVAX may not result in protection of all vaccine recipients.

5.5 Concurrent Illness

Vaccination should be deferred in patients with active untreated tuberculosis. Deferral should be considered in acute illness, for example, in the presence of fever.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

6.1.1 Shingles Prevention Study

In clinical trials, ZOSTAVAX has been evaluated for safety in approximately 21,000 adults. In the largest of these trials, the Shingles Prevention Study (SPS), subjects received a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276). The racial distribution across both vaccination groups was similar: White (95%); Black (2.0%); Hispanic (1.0%) and Other (1.0%) in both vaccination groups. The gender distribution was 59% male and 41% female in both vaccination groups. The age distribution of subjects enrolled, 59-99 years, was similar in both vaccination groups.

The Adverse Event Monitoring Substudy of the SPS, designed to provide detailed data on the safety profile of the zoster vaccine (n=3,345 received ZOSTAVAX and n=3,271 received placebo) used vaccination report cards (VRC) to record adverse events occurring from Days 0 to 42 postvaccination (97% of subjects completed VRC in both vaccination groups). In addition, monthly surveillance for hospitalization was conducted through the end of the study, 2 to 5 years postvaccination.

The remainder of subjects in the SPS (n=15,925 received ZOSTAVAX and n=16,005 received placebo) were actively followed for safety outcomes through Day 42 postvaccination and passively followed for safety after Day 42.

Serious Adverse Events Occurring 0-42 Days Postvaccination

In the overall SPS study population, serious adverse events occurred at a similar rate (1.4%) in subjects vaccinated with ZOSTAVAX or placebo.

In the AE Monitoring Substudy, the rate of SAEs was increased in the group of subjects who received ZOSTAVAX as compared to the group of subjects who received placebo (Table 1).

Table 1: Number of Subjects with ≥1 Serious Adverse Events (0-42 Days Postvaccination) in the Shingles Prevention Study

Cohort	ZOSTAVAX	Placebo	Relative Risk (95% CI)
	n/N %	n/N %	
Overall Study Cohort (all ages)	255/18671 1.4%	254/18717 1.4%	1.01 (0.85, 1.20)
60-69 years old	113/10100 1.1%	101/10095 1.0%	1.12 (0.86, 1.46)
70-79 years old	115/7351 1.6%	132/7333 1.8%	0.87 (0.68, 1.11)
≥80 years old	27/1220 2.2%	21/1289 1.6%	1.36 (0.78, 2.37)
AE Monitoring Substudy Cohort (all ages)	64/3326 1.9%	41/3249 1.3%	1.53 (1.04, 2.25)
60-69 years old	22/1726 1.3%	18/1709 1.1%	1.21 (0.66, 2.23)
70-79 years old	31/1383 2.2%	19/1367 1.4%	1.61 (0.92, 2.82)
≥80 years old	11/217 5.1%	4/173 2.3%	2.19 (0.75, 6.45)

N=number of subjects in cohort with safety follow-up
n=number of subjects reporting an SAE 0-42 Days postvaccination

Among reported serious adverse events in the SPS (Days 0 to 42 postvaccination), serious cardiovascular events occurred more frequently in subjects who received ZOSTAVAX (20 [0.6%]) than in subjects who received placebo (12 [0.4%]) in the AE Monitoring Substudy. The frequencies of serious cardiovascular events were similar in subjects who received ZOSTAVAX (81 [0.4%]) and in subjects who received placebo (72 [0.4%]) in the entire study cohort (Days 0 to 42 postvaccination).

Serious Adverse Events Occurring Over the Entire Course of the Study

Rates of hospitalization were similar among subjects who received ZOSTAVAX and subjects who received placebo in the AE Monitoring Substudy, throughout the entire study.

Fifty-one individuals (1.5%) receiving ZOSTAVAX were reported to have congestive heart failure (CHF) or pulmonary edema compared to 39 individuals (1.2%) receiving placebo in the AE Monitoring Substudy; 58 individuals (0.3%) receiving ZOSTAVAX were reported to have congestive heart failure (CHF) or pulmonary edema compared to 45 (0.2%) individuals receiving placebo in the overall study.

In the SPS, all subjects were monitored for vaccine-related SAEs. Investigator-determined, vaccine-related serious adverse experiences were reported for 2 subjects vaccinated with ZOSTAVAX (asthma exacerbation and polymyalgia rheumatica) and 3 subjects who received placebo (Goodpasture's syndrome, anaphylactic reaction, and polymyalgia rheumatica).

Deaths

The incidence of death was similar in the groups receiving ZOSTAVAX or placebo during the Days 0-42 postvaccination period; 14 deaths occurred in the group of subjects who received ZOSTAVAX and 16 deaths occurred in the group of subjects who received placebo. The most common reported cause of death was cardiovascular disease (10 in the group of subjects who received ZOSTAVAX, 8 in the group of subjects who received placebo). The overall incidence of death occurring at any time during the study was similar between vaccination groups: 793 deaths (4.1%) occurred in subjects who received ZOSTAVAX and 795 deaths (4.1%) in subjects who received placebo.

Most Common Adverse Reactions

Adverse Events Reported in the AE Monitoring Substudy of the SPS

Injection-site and systemic adverse events reported at an incidence $\geq 1\%$ are shown in Table 2. Most of these adverse events were reported as mild in intensity. The overall incidence of vaccine-related injection-site adverse reactions was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (48% for ZOSTAVAX and 17% for placebo).

Table 2: Injection-Site and Systemic Adverse Experiences Reported by Vaccine Report Card in $\geq 1\%$ of Adults Who Received ZOSTAVAX or Placebo (0-42 Days Postvaccination) in the AE Monitoring Substudy of the Shingles Prevention Study

Adverse Experience	ZOSTAVAX (N = 3345)	Placebo (N = 3271)
	%	%
<i>Injection Site</i>	33.7	6.4
Erythema*	33.4	8.3
Pain/tenderness*	24.9	4.3
Swelling*	1.4	1.4
Hematoma	6.6	1.0
Pruritus	1.5	0.3
Warmth		
<i>Systemic</i>		
Headache	1.4	0.8

*Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 0-4 postvaccination.

The numbers of subjects with elevated temperature ($\geq 38.3^{\circ}\text{C}$ [$\geq 101.0^{\circ}\text{F}$]) within 42 days postvaccination were similar in the ZOSTAVAX and the placebo vaccination groups [27 (0.8%) vs. 27 (0.9%), respectively].

The following adverse experiences in the AE Monitoring Substudy of the SPS (Days 0 to 42 postvaccination) were reported at an incidence $\geq 1\%$ and greater in subjects who received ZOSTAVAX than in subjects who received placebo, respectively: respiratory infection (65 [1.9%] vs. 55 [1.7%]), fever (59 [1.8%] vs. 53 [1.6%]), flu syndrome (57 [1.7%] vs. 52 [1.6%]), diarrhea (51 [1.5%] vs. 41 [1.3%]), rhinitis (46 [1.4%] vs. 36 [1.1%]), skin disorder (35 [1.1%] vs. 31 [1.0%]), respiratory disorder (35 [1.1%] vs. 27 [0.8%]), asthenia (32 [1.0%] vs. 14 [0.4%]).

6.1.2 VZV Rashes Following Vaccination

Within the 42-day post vaccination reporting period in the SPS, non-injection-site zoster-like rashes were reported by 53 subjects (17 for ZOSTAVAX and 36 for placebo). Of 41 specimens that were adequate for Polymerase Chain Reaction (PCR) testing, wild-type

VZV was detected in 25 (5 for ZOSTAVAX, 20 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

Of reported varicella-like rashes (n=59), 10 had specimens that were available and adequate for PCR testing. VZV was not detected in any of these specimens.

In clinical trials in support of the initial licensure of the frozen formulation of ZOSTAVAX, the reported rates of noninjection-site zoster-like and varicella-like rashes within 42 days postvaccination were also low in both zoster vaccine and placebo recipients. Of 17 reported varicella-like rashes and noninjection-site, zoster-like rashes, 10 specimens were available and adequate for PCR testing. The Oka/Merck strain was identified by PCR analysis from the lesion specimens of two subjects who reported varicella-like rashes (onset on Day 8 and 17).

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-marketing use of ZOSTAVAX. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Skin and subcutaneous tissue disorders: rash

Musculoskeletal and connective tissue disorders: arthralgia; myalgia

General disorders and administration site conditions: injection-site rash; injection-site urticaria; pyrexia; transient injection-site lymphadenopathy

Immune system disorders: hypersensitivity reactions including anaphylactic reactions

Reporting Adverse Events

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report online to www.vaers.hhs.gov.²

7 DRUG INTERACTIONS

Concurrent administration of ZOSTAVAX and antiviral medications known to be effective against VZV has not been evaluated.

7.1 Concomitant Administration with Other Vaccines

For administration of ZOSTAVAX with trivalent inactivated influenza vaccine, [see *Clinical Studies (14)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with ZOSTAVAX. It is also not known whether ZOSTAVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally occurring VZV infection is known to sometimes cause fetal harm. ZOSTAVAX is not indicated in women of child-bearing age and should not be administered to pregnant females.

Vaccinees and health care providers are encouraged to report any exposure to ZOSTAVAX during pregnancy by calling (800) 986-8999.

8.3 Nursing Mothers

ZOSTAVAX is not indicated in women who are nursing. It is not known whether VZV is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if ZOSTAVAX is administered to a nursing woman.

8.4 Pediatric Use

ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox) and should not be used in children and adolescents.

8.5 Geriatric Use

The median age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX was 69 years (range 59-99 years). Of the 19,270 subjects who received ZOSTAVAX, 10,378 were 60-69 years of age, 7,629 were 70-79 years of age, and 1,263 were 80 years of age or older.

11 DESCRIPTION

ZOSTAVAX is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). ZOSTAVAX, when reconstituted as directed, is a sterile suspension for subcutaneous administration. Each 0.65-mL dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck strain of VZV when reconstituted and stored at room temperature for up to 30 minutes.

Each dose contains 31.16 mg of sucrose, 15.58 mg of hydrolyzed porcine gelatin, 3.99 mg of sodium chloride, 0.62 mg of monosodium L-glutamate, 0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium

chloride; residual components of MRC5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum. The product contains no preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The risk of developing zoster appears to be related to a decline in VZV-specific immunity. ZOSTAVAX was shown to boost VZV-specific immunity, which is thought to be the mechanism by which it protects against zoster and its complications. [See *Clinical Studies* (14).]

Herpes zoster (HZ), commonly known as shingles or zoster, is a manifestation of the reactivation of varicella zoster virus (VZV), which, as a primary infection, produces chickenpox (varicella). Following initial infection, the virus remains latent in the dorsal root or cranial sensory ganglia until it reactivates, producing zoster. Zoster is characterized by a unilateral, painful, vesicular cutaneous eruption with a dermatomal distribution.

Pain associated with zoster may occur during the prodrome, the acute eruptive phase, and the postherpetic phase of the infection. Pain occurring in the postherpetic phase of infection is commonly referred to as postherpetic neuralgia (PHN).

Serious complications, such as PHN, scarring, bacterial superinfection, allodynia, cranial and motor neuron palsies, pneumonia, encephalitis, visual impairment, hearing loss, and death can occur as the result of zoster.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ZOSTAVAX has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

14 CLINICAL STUDIES

Efficacy of ZOSTAVAX was evaluated in the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial in which 38,546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276). Subjects were followed for the development of zoster for a median of 3.1 years (range 31 days to 4.90 years). The study excluded people who were immunocompromised or using corticosteroids on a regular basis, anyone with a previous history of HZ, and those with conditions that might interfere with study evaluations, including people with cognitive impairment, severe hearing loss, those who were non-ambulatory and those whose survival was not considered to be at least 5 years. Randomization was stratified by age, 60-69 and ≥70 years of age. Suspected zoster cases were confirmed by Polymerase Chain Reaction (PCR) [93%], viral culture [1%], or in the absence of viral detection, as determined by the Clinical Evaluation Committee [6%]. Individuals in both vaccination groups who developed zoster were given famciclovir, and, as necessary, pain medications. The primary efficacy analysis included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination (Modified Intent-To-Treat [MITT] analysis).

ZOSTAVAX significantly reduced the risk of developing zoster when compared with placebo (Table 3). Vaccine efficacy for the prevention of HZ was highest for those subjects 60-69 years of age and declined with increasing age.

Table 3: Efficacy of ZOSTAVAX on HZ Incidence Compared with Placebo in the Shingles Prevention Study*

Age group [†] (yrs.)	ZOSTAVAX			Placebo			Vaccine Efficacy (95% CI)
	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	
Overall	19254	315	5.4	19247	642	11.1	51% (44%, 58%)
60-69	10370	122	3.9	10356	334	10.8	64% (56%, 71%)
70-79	7621	156	6.7	7559	261	11.4	41% (28%, 52%)
≥80	1263	37	9.9	1332	47	12.2	18% (-29%, 48%)

*The analysis was performed on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

[†]Age strata at randomization were 60-69 and ≥70 years of age.

Forty-five subjects were excluded from the MITT analysis (16 in the group of subjects who received ZOSTAVAX and 29 in the group of subjects who received placebo), including 24 subjects with evaluable HZ cases that occurred in the first 30 days postvaccination (6 evaluable HZ cases in the group of subjects who received ZOSTAVAX and 18 evaluable HZ cases in the group of subjects who received placebo).

Suspected HZ cases were followed prospectively for the development of HZ-related complications. Table 4 compares the rates of PHN defined as HZ-associated pain (rated as 3 or greater on a 10-point scale by the study subject and occurring or persisting at least 90 days) following the onset of rash in evaluable cases of HZ.

Table 4: Postherpetic Neuralgia (PHN)* in the Shingles Prevention Study†

Age group (yrs.)‡	ZOSTAVAX					Placebo					Vaccine efficacy against PHN in subjects who develop HZ postvaccination (95% CI)
	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person- yrs.	% HZ cases with PHN	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person- yrs.	% HZ cases with PHN	
Overall	19254	315	27	0.5	8.6%	19247	642	80	1.4	12.5%	39%§ (7%, 59%)
60-69	10370	122	8	0.3	6.6%	10356	334	23	0.7	6.9%	5% (-107%, 56%)
70-79	7621	156	12	0.5	7.7%	7559	261	45	2.0	17.2%	55% (18%, 76%)
≥80	1263	37	7	1.9	18.9%	1332	47	12	3.1	25.5%	26% (-69%, 68%)

*PHN was defined as HZ-associated pain rated as ≥3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of HZ rash using Zoster Brief Pain Inventory (ZBPI)³.

†The table is based on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

‡Age strata at randomization were 60-69 and ≥70 years of age.

§Age-adjusted estimate based on the age strata (60-69 and ≥70 years of age) at randomization.

The median duration of clinically significant pain (defined as ≥3 on a 0-10 point scale) among HZ cases in the group of subjects who received ZOSTAVAX as compared to the group of subjects who received placebo was 20 days vs. 22 days based on the confirmed HZ cases.

Overall, the benefit of ZOSTAVAX in the prevention of PHN can be primarily attributed to the effect of the vaccine on the prevention of herpes zoster. Vaccination with ZOSTAVAX in the SPS reduced the incidence of PHN in individuals 70 years of age and older who developed zoster postvaccination. Other prespecified zoster-related complications were reported less frequently in subjects who received ZOSTAVAX compared to subjects who received placebo. Among HZ cases, zoster-related complications were reported at similar rates in both vaccination groups (Table 5).

Table 5: Specific complications* of zoster among HZ cases in the Shingles Prevention Study

Complication	ZOSTAVAX (N = 19,270)		Placebo (N = 19,276)	
	(n = 321)	% Among Zoster Cases	(n = 659)	% Among Zoster Cases
Allodynia	135	42.1	310	47.0
Bacterial Superinfection	3	0.9	7	1.1
Dissemination	5	1.6	11	1.7
Impaired Vision	2	0.6	9	1.4
Ophthalmic Zoster	35	10.9	69	10.5
Peripheral Nerve Palsies (motor)	5	1.6	12	1.8
Ptosis	2	0.6	9	1.4
Scarring	24	7.5	57	8.6
Sensory Loss	7	2.2	12	1.8

N=number of subjects randomized

n=number of zoster cases, including those cases occurring within 30 days postvaccination, with these data available

*Complications reported at a frequency of ≥1% in at least one vaccination group among subjects with zoster.

Visceral complications reported by fewer than 1% of subjects with zoster included 3 cases of pneumonitis and 1 case of hepatitis in the placebo group, and 1 case of meningoencephalitis in the vaccine group.

Immune responses to vaccination were evaluated in a subset of subjects enrolled in the Shingles Prevention Study (N=1395). VZV antibody levels (Geometric Mean Titers, GMT), as measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) 6

weeks postvaccination, were increased 1.7-fold (95% CI: [1.6 to 1.8]) in the group of subjects who received ZOSTAVAX compared to subjects who received placebo; the specific antibody level that correlates with protection from zoster has not been established. In a double-blind, controlled substudy, 374 adults in the US, 60 years of age and older (median age = 66 years), were randomized to receive trivalent inactivated influenza vaccine (TIV) and ZOSTAVAX concurrently (N=188), or TIV alone followed 4 weeks later by ZOSTAVAX alone (N=186). The antibody responses to both vaccines at 4 weeks postvaccination were similar in both groups.

15 REFERENCES

1. Reitschel RL, Bernier R. Neomycin sensitivity and the MMR vaccine. JAMA 1981;245(6):571.
2. Atkinson WL, Pickering LK, Schwartz B, Weniger BG, Iskander JK, Watson JC. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR02):1-36.
3. Coplan PM, Schmader K, Nikas A, Chan ISF, Choo P, Levin MJ, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: Adaptation of the brief pain inventory. J Pain 2004;5(6):344-56.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4963-00 — ZOSTAVAX is supplied as follows: (1) a package of 1 single-dose vial of lyophilized vaccine, NDC 0006-4963-00 (package A); and (2) a separate package of 10 vials of diluent (package B).

No. 4963-41 — ZOSTAVAX is supplied as follows: (1) a package of 10 single-dose vials of lyophilized vaccine, NDC 0006-4963-41 (package A); and (2) a separate package of 10 vials of diluent (package B).

Handling and Storage

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of -15°C (+5°F) or colder.

ZOSTAVAX SHOULD BE STORED FROZEN at an average temperature of -15°C (+5°F) or colder until it is reconstituted for injection. Any freezer, including frost-free, that has a separate sealed freezer door and reliably maintains an average temperature of -15°C or colder is acceptable for storing ZOSTAVAX.

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

Before reconstitution, protect from light.

The diluent should be stored separately at room temperature (20 to 25°C, 68 to 77°F), or in the refrigerator (2 to 8°C, 36 to 46°F).

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.2).]

17.1 Instructions

The health care provider should question the vaccine recipient about reactions to previous vaccines. The health care provider should also inform the vaccine recipient of the benefits and risks of ZOSTAVAX. Patients should be provided with a copy of the Patient Information about ZOSTAVAX at the end of this insert, and be given an opportunity to discuss any questions or concerns.

Vaccinees should also be informed of the potential risk of transmitting the vaccine virus to varicella-susceptible individuals, including pregnant women who have not had chickenpox.

Patients should be instructed to report any adverse reactions to their health care provider.

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17.2 FDA-Approved Patient Labeling

Patient Information about

ZOSTAVAX® (pronounced "ZOS tah vax")

Generic name: Zoster Vaccine Live

You should read this summary of information about ZOSTAVAX¹ before you are vaccinated. If you have any questions about ZOSTAVAX after reading this leaflet, you should ask your health care provider. This information does not take the place of talking about ZOSTAVAX with your doctor, nurse, or other health care provider. Only your health care provider can decide if ZOSTAVAX is right for you.

What is ZOSTAVAX and how does it work?

ZOSTAVAX is a vaccine that is used for adults 60 years of age or older to prevent shingles (also known as zoster).

ZOSTAVAX contains a weakened chickenpox virus (varicella-zoster virus).

ZOSTAVAX works by helping your immune system protect you from getting shingles. If you do get shingles even though you have been vaccinated, ZOSTAVAX may help prevent the nerve pain that can follow shingles in some people.

ZOSTAVAX may not protect everyone who gets the vaccine. ZOSTAVAX cannot be used to treat shingles once you have it.

What do I need to know about shingles and the virus that causes it?

Shingles is caused by the same virus that causes chickenpox. Once you have had chickenpox, the virus can stay in your nervous system for many years. For reasons that are not fully understood, the virus may become active again and give you shingles. Age and problems with the immune system may increase your chances of getting shingles.

Shingles is a rash that is usually on one side of the body. The rash begins as a cluster of small red spots that often blister. The rash can be painful. Shingles rashes usually last up to 30 days and, for most people, the pain associated with the rash lessens as it heals.

Who should not get ZOSTAVAX?

You should not get ZOSTAVAX if you:

- are allergic to any of its ingredients.
- are allergic to gelatin or neomycin.
- have a weakened immune system (for example, an immune deficiency, leukemia, lymphoma, or HIV/AIDS).
- take high doses of steroids by injection or by mouth.
- are pregnant or plan to get pregnant.

You should not get ZOSTAVAX to prevent chickenpox.

Children should not get ZOSTAVAX.

How is ZOSTAVAX given?

ZOSTAVAX is given as a single dose by injection under the skin.

What should I tell my health care provider before I get ZOSTAVAX?

You should tell your health care provider if you:

- have or have had any medical problems.
- take any medicines, including non-prescription medicines, and dietary supplements.
- have any allergies, including allergies to neomycin or gelatin.
- had an allergic reaction to another vaccine.
- are pregnant or plan to become pregnant.
- are breast-feeding.

Tell your health care provider if you expect to be in close contact (including household contact) with newborn infants, someone who may be pregnant and has not had chickenpox or been vaccinated against chickenpox, or someone who has problems with their immune system. Your health care provider can tell you what situations you may need to avoid.

What are the possible side effects of ZOSTAVAX?

The most common side effects that people in the clinical studies reported after receiving the vaccine include:

- redness, pain, itching, swelling, warmth, or bruising where the shot was given.
- headache.

The following additional side effects have been reported in general use with ZOSTAVAX:

- allergic reactions, which may be serious and may include difficulty in breathing or swallowing. If you have an allergic reaction, call your doctor right away.
- fever
- hives at the injection site
- joint pain
- muscle pain
- rash
- rash at the injection site
- swollen glands near the injection site (that may last a few days to a few weeks)

Tell your healthcare provider if you have any new or unusual symptoms after you receive ZOSTAVAX.

What are the ingredients of ZOSTAVAX?

Active Ingredient: a weakened form of the varicella-zoster virus.

Inactive Ingredients: sucrose, hydrolyzed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride.

What else should I know about ZOSTAVAX?

Vaccinees and their health care providers are encouraged to call (800) 986-8999 to report any exposure to ZOSTAVAX during pregnancy.

This leaflet summarizes important information about ZOSTAVAX.

If you would like more information, talk to your health care provider or visit the website at www.ZOSTAVAX.com or call 1-800-622-4477.

Rx Only

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This is a representative sample of the packaging. Not inclusive of labeling.

PRINCIPAL DISPLAY PANEL - VIAL LABEL - 1 SINGLE-DOSE VIAL (0.65 mL)

1 Single-dose Vial (0.65 mL)

Zoster Vaccine Live

ZOSTAVAX®

STORE FROZEN

Rx only

U.S. Govt. Lic. No. 2

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PRINCIPAL DISPLAY PANEL - CARTON - 1 SINGLE DOSE VIAL (0.65 mL)

A

NDC 0006-4963-00

1 Single-dose Vial (0.65 mL)

Zoster Vaccine Live

ZOSTAVAX®

STORE FROZEN

Oka/Merck strain. Human diploid cell (MRC-5) culture origin. Each 0.65-mL dose contains a minimum of 19,400 PFU (plaque-forming units).

Contains no preservative.

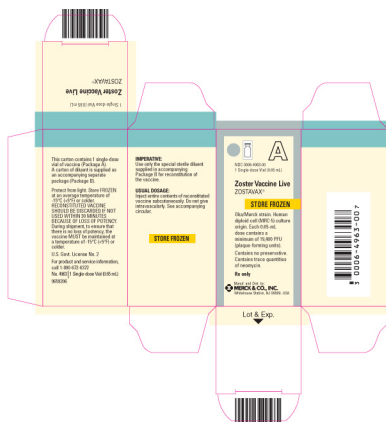
Contains trace quantities of neomycin.

Rx only

Manuf. and Dist. by:

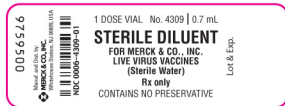
MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA



PRINCIPAL DISPLAY PANEL - VIAL LABEL - STERILE DILUENT 1 DOSE VIAL 0.7 mL

1 DOSE VIAL
 No. 4309 | 0.7 mL
 STERILE DILUENT
 FOR MERCK & CO., INC.
 LIVE VIRUS VACCINES
 (Sterile Water)
 Rx only
 CONTAINS NO PRESERVATIVE



PRINCIPAL DISPLAY PANEL - CARTON - STERILE DILUENT 10-0.7 mL VIALS

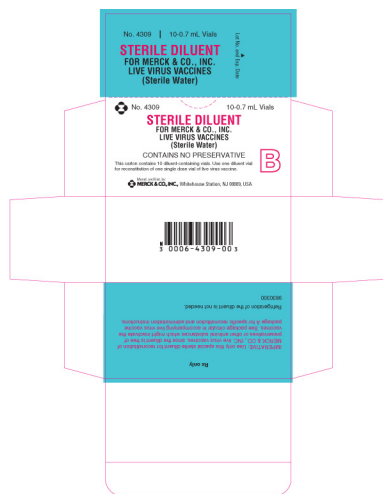
No. 4309
 10-0.7 mL Vials
 STERILE DILUENT
 FOR MERCK & CO., INC.
 LIVE VIRUS VACCINES
 (Sterile Water)
 CONTAINS NO PRESERVATIVE

B

This carton contains 10 diluent-containing vials. Use one diluent vial for reconstitution of one single dose vial of live virus vaccine.

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